EXHIBIT E

Original Article

N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer

A Longitudinal Cohort Study Based on German Health Insurance Data

Willy Gomm, Christoph Röthlein, Katrin Schüssel, Gabriela Brückner, Helmut Schröder, Steffen Heß, Roland Frötschl, Karl Broich, Britta Haenisch

Summary

Background: N-Nitrosodimethylamine (NDMA), classified as a probable human carcinogen, has been found as a contaminant in the antihypertensive drug valsartan. Potentially carcinogenic effects associated with the consumption of NDMA-contaminated valsartan have not yet been analyzed in large-scale cohort studies. We therefore carried out the study reported here to explore the association between NDMA-contaminated valsartan and the risk of cancer.

Methods: This cohort study was based on longitudinal routine data obtained from a large German statutory health insurance provider serving approximately 25 million insurees. The cohort comprised patients who had filled a prescription for valsartan in the period 2012–2017. The endpoint was an incident diagnosis of cancer. Hazard ratios (HR) for cancer in general and for certain specific types of cancer were calculated by means of Cox regression models with time-dependent variables and adjustment for potential confounders.

Results: A total of 780 871 persons who had filled a prescription for valsartan between 2012 and 2017 were included in the study. There was no association between exposure to NDMA-contaminated valsartan and the overall risk of cancer. A statistically significant association was found, however, between exposure to NDMA-contaminated valsartan and hepatic cancer (adjusted HR 1.16; 95% confidence interval [1.03; 1.31]).

Conclusion: These findings suggest that the consumption of NDMA-contaminated valsartan is associated with a slightly increased risk of hepatic cancer; no association was found with the risk of cancer overall. Close observation of the potential long-term effects of NDMA-contaminated valsartan seems advisable.

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German Center for Neurodegenerative Diseases (DZNE) e. V., Bonn:
Dr. rer. nat. Willy Gomm, Dr. rer. nat. Christoph Röthlein, Prof. Dr. rer. nat. Britta Haenisch

AOK Research Institute (WIdO), Berlin: Dr. phil. nat. Katrin Schüssel, Gabriela Brückner, Dipl.-Inform., Helmut Schröder, Dipl.-Soz.

Federal Institute for Drugs and Medical Devices (BfArM), Bonn: Dr. rer. nat. Steffen Heß, Dr. rer. nat. Roland Frötschl, Prof. Dr. med. Karl Broich, Prof. Dr. rer. nat. Britta Haenisch

Center for Translational Medicine, University Hospital Bonn: Prof. Dr. rer. nat. Britta Haenisch

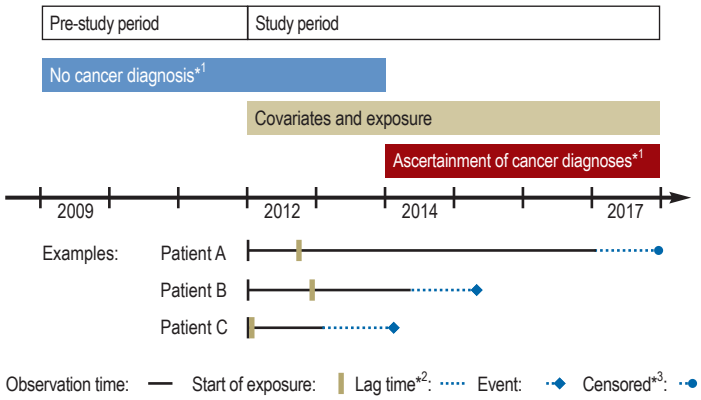
The angiotensin II receptor antagonist valsartan is used predominantly to treat hypertension and heart failure (1–4). In 2018, N-nitrosodimethylamine (NDMA) was detected in the valsartan active substance manufactured by Zhejiang Pharmaceuticals (5,6). Preparations containing the contaminated valsartan were withdrawn from the market by regulatory agencies across the world (5,7). In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) ordered the recall of drug products contaminated with NDMA in July 2018. The NDMA contamination seems to be the result of a change in the manufacturing process in 2012 (8). Thus, patients may have been exposed to contaminated valsartan from 2012 until the recall. Investigations of other sartans with a tetrazole ring structure have revealed contamination with no more than small amounts of NDMA in only a few cases. NDMA is one of the most potent mutagenic carcinogens in animal models and was classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (9–11).

A Danish cohort study based on healthcare system registry data reported no statistically significantly elevated overall risk of cancer and no increase in the risk of some individual cancers after exposure to drug products containing NDMA-contaminated valsartan (12). However, the sample size of the Danish study was limited to a total of 5150 patients, which may explain the non-significance of the results (12). For our cohort study we used a large longitudinal sample from the AOK, a large German statutory health insurance fund. We examined the association between filled prescriptions of potentially NDMA-contaminated valsartan drug product prescription and cancer risk in comparison with non-contaminated valsartan. Our results provide insights based on a substantially higher number of patients than in the Danish study. We also focus on various cancer outcomes with a large number of cancer events.

Methods

The *Figure* provides an overview of the study design. The data set comprises health insurance data from the AOK. It includes all patients aged 40 years or older at the beginning of 2012 who filled at least one prescription of valsartan between 1 January 2012 and 31

FIGURE



Overview of the study design

*1 For the evaluation of long-term use (3 years) the absence of cancer until the end of 2014 was required; follow-up started at the beginning of 2015.

*2 Depicted is the lag time of the main analysis (lag time of 1 year); for the evaluation of long-term use (3 years), no lag time was included.

*3 Data censored because of death, end of insurance cover, or end of study.

December 2017. Potential NDMA contamination was assessed on the basis of the pharmaceutical registration number (PZN) as product identifier in the filled prescription records and information on valsartan drug products from marketing authorization holders. The outcome was an incident cancer diagnosis. Cox regression models with time-varying variables and adjustment for potential influencing factors were used to calculate hazard ratios (HR) for cancer overall and for several individual cancer types. Detailed information can be found in the *eMethods*.

Results

The study cohort comprised 780 871 persons with a filled valsartan prescription during the period 2012–2017. Of these, 409 183 were classified as ever and 371 688 as never exposed to potentially NDMA-contaminated valsartan. The characteristics of the study cohort in 2012 are presented in *Table 1*. The mean and median person-times were 3.1 years (standard deviation 1.5 years) and 3.25 years (interquartile range 2–4.75), respectively.

For the outcome cancer overall, exposure to potentially NDMA-contaminated valsartan was not associated with an increased risk of an incident cancer diagnosis in comparison with exposure to non-contaminated valsartan (adjusted HR 1.00, 95% confidence interval [0.98; 1.02]; *eTable 1*). A similar result was obtained after adjustment for age and gender only (HR 1.01 [0.99; 1.03]). Based on the manufacturers' information about the packages of valsartan drug products sold, we were able to classify the filled valsartan prescriptions into different degrees of likelihood of contamination, from possibly to probably contaminated with NDMA *(eMethods)*. Exposure to neither possibly (adjusted HR 1.00 [0.97; 1.03]; *eTable 1*) nor probably (adjusted HR 0.99 [0.97; 1.02]; *eTable 1*) NDMA-contaminated valsartan was associated with the endpoint cancer overall. Differentiation between prevalent and incident exposure to potentially NDMA-contaminated valsartan showed no association with the endpoint cancer overall in either case (adjusted HR 0.97 [0.94; 1.01] and adjusted HR 1.01 [0.98 to 1.04], respectively; *eTable 1*). Higher exposure to potentially NDMA-contaminated valsartan, based on defined daily doses (DDDs), had no effect on the overall cancer rate *(eTable 1)*. For sensitivity analyses, the lag time between the last quarter assessed for exposure status and the initial cancer diagnosis or the end of the person-time was varied from 6 months to 2 years. We observed no significant differences across this lag time spectrum *(eTable 2)*. In a separate analysis we examined long-term use of valsartan, defined as filling of valsartan prescriptions in at least nine quarters of the first 3 years of the study period. Long-term use showed no association with the change in overall cancer rate (adjusted HR 0.96 [0.89; 1.04]); neither were dose-dependent effects observed *(eTable 1)*.

The analysis of individual cancer types showed a significant association between potentially NDMA-contaminated valsartan and liver cancer (adjusted HR 1.16 [1.03; 1.31], p = 0.017; *Table 2*). No association with potentially NDMA-contaminated valsartan exposure was detected for any other cancer outcomes *(Table 3)*. The association with liver cancer remained stable after basic adjustment for age and gender (HR 1.20 [1.06; 1.35]) and also after additional adjustment for hepatitis (ICD-10 codes B15–B19) and other liver diseases (ICD-10 codes K70–K76, Z944). Following correction for age and gender there was an increase from 34.6 to 39.1 per 100 000 person-years in the incidence rate of liver cancer for the valsartan-exposed population above 40 years of age according to the 2011 German census. However, no dose-dependent effect on the risk of liver cancer was found for higher exposure to potentially NDMA-contaminated valsartan *(Table 2)*. Varying lag times of 6 months to 2 years also did not alter the effect *(eTable 2)*. Evaluation of 3-year long-term use of potentially NDMA-contaminated valsartan resulted in a decreased sample size (75 112 patients, 130 cases of liver cancer) and showed no significant association with liver cancer (adjusted HR 1.22 [0.80; 1.89]; *Table 2*). The incidence rates for exposure and no exposure are given in *eTable 1* and *Table 2*.

Discussion

In our study we observed a slight elevation in the risk of liver cancer with the use of potentially NDMA-contaminated valsartan. Our analysis is based on a large longitudinal data set from a large statutory health insurance provider and on detailed information about potentially NDMA-contaminated valsartan from the marketing authorization holders of valsartan drug products.

Comparison with other studies on valsartan exposure

Only one cohort study on this topic has been published to date (12); the Danish registry study by Pottegard et al. has only a small sample size, comprising 5150 persons with prescription of valsartan. Our study contains around 150 times more persons with valsartan prescription. Pottegard et al. examined effects on the overall cancer rate and individual cancers, finding no statistically significant associations (HR for cancer overall 1.09 [0.85; 1.41] (12). However, the number of cancer cases in the Danish study was limited (302 cancers overall; only eight cases each of kidney and bladder cancer). The statistical power for detection of small effects is therefore limited, and no precise statements on small effect sizes can be made. With regard to qualitative effects, our findings are in agreement with the Danish study, as we detected no modification of cancer risk by potentially NDMA-contaminated valsartan for cancer overall or for the individual cancer types examined by the Danish authors.

For liver cancer, however, we observed a statistically significant association. This is interesting, as from a biological perspective liver cancer is the most likely form of cancer to resulting from NDMA contamination. That is the reason why we classified the occurrence of liver cancer as an independent primary endpoint compared with other specific types of cancer. Pottegard et al. did not report results for liver cancer, because no cases of liver cancer were detected among the persons who had received potentially NDMA-contaminated valsartan in the Danish study (12).

TABLE 1

Baseline characteristics of the study cohort

Characteristic		All (N = 780 871) (%)	NDMA exposure	
			Not exposed (n = 371 688) (%)	Exposed (n = 409 183) (%)
Gender	Male	312 146 (40.0)	156 360 (42.1)	155 786 (38.1)
	Female	468 725 (60.0)	215 328 (57.9)	253 397 (61.9)
Age: median (IQR)		68 (57–75)	66 (55–74)	69 (58–76)
Prevalent use	No	534 519 (68.5)	300 370 (80.8)	234 149 (57.2)
	Yes	246 352 (31.5)	71 318 (19.2)	175 034 (42.8)
SSRI		36 825 (4.7)	16 202 (4.4)	20 623 (5.0)
NSAID		316 350 (40.5)	150 730 (40.6)	165 620 (40.5)
5α-Reductase inhibitors		6136 (0.8)	2684 (0.7)	3452 (0.8)
Low-dose ASA		94 061 (12.0)	38 988 (10.5)	55 073 (13.5)
Statins		237 998 (30.5)	102 502 (27.6)	135 496 (33.1)
Spironolactone		25 235 (3.2)	9986 (2.7)	15 249 (3.7)
Glucocorticoids		72 493 (9.3)	32 805 (8.8)	39 688 (9.7)
Hormone replacement therapy		19 219 (2.5)	9025 (2.4)	10 194 (2.5)
Polypharmacy		456 508 (58.5)	197 710 (53.2)	258 798 (63.2)
Diabetes		277 266 (35.5)	125 388 (33.7)	151 878 (37.1)
COPD		103 474 (13.3)	45 356 (12.2)	58 118 (14.2)
Congestive heart failure		136 566 (17.5)	55 554 (14.9)	81 012 (19.8)
Alcohol-related disease		13 512 (1.7)	6665 (1.8)	6847 (1.7)
CCI	Low (0)	227 331 (29.1)	121 183 (32.6)	106 148 (25.9)
	Medium (1–2)	333 351 (42.7)	158 327 (42.6)	175 024 (42.8)
	High (≥ 3)	220 189 (28.2)	92 178 (24.8)	128 011 (31.3)

ASA, Acetylsalicylic acid; CCI, Charlson comorbidity index; COPD, chronic-obstructive pulmonary disease; IQR, interquartile range; NDMA, N-nitrosodimethylamine; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors

Strengths and limitations of the study

The main strength of our study is the cohort size of 780 871 persons with valsartan prescription and longitudinal health insurance claims data information from 2009 to 2017, drawn from the almost one third of the German population insured by the AOK (13, 14). This allowed us to perform analyses in an unselected patient population in a real-life setting, thus avoiding recall and selection bias. Another strength is that we received detailed information from the marketing authorization holders—e.g., which batches were produced with valsartan from Zhejiang Pharmaceuticals and how many packages were sold. These items of information are not included in the health insurance data. This enabled us to calculate the proportion of all batches with the relevant pharmaceutical registration numbers in Germany that contained potentially NDMA-contaminated valsartan.

The study also features limitations. Because the study is based on observational health insurance claims data (i.e., on non-randomized data), we cannot rule out residual confounding. Although we adjusted our analysis by including numerous potential influencing factors, some risk factors for cancer, such as smoking habits, nutritional habits, and genetic predisposition, are not available in routine health insurance data and, therefore, could not be integrated into the analysis. Nevertheless, the frequency of unmeasured cancer risk factors should be similar in the NDMA-exposed and non-exposed groups. However, we cannot rule out unmeasured confounders such as group differences in adherence patterns, due for instance to polypharmacy or differences in the Charlson comorbidity index. Inclusion of prevalent users did not alter the result. We detected only marginal differences between results with basic adjustment for age and gender and the fully adjusted model with all covariates. This indicates that the potentially influential factors included in the model had no strong effects. Although detailed batch-wise information on potentially NDMA-contaminated valsartan was provided, we had no information on the exact NDMA content of individual valsartan tablets. However, sensitivity analyses with varying degrees of possible or probable NDMA contamination yielded results comparable to those of the main analysis. A further limitation is that due to the limited follow-up time we were not able to monitor the long-term effects of

TABLE 2

Liver cancer risk due to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

	Hazard ratio [95% CI][*1]	Sample size/ Cancer cases
Exposure to NDMA-contaminated valsartan		
No exposure	1.00 (ref)	354 628/444
Exposure	1.16 [1.03; 1.31]	385 167/736
Exposure in dose categories		
0 to ≤ 90 DDD	1.15 [0.98; 1.34]	122 479/244
> 90 to ≤ 170 DDD	1.19 [1.02; 1.40]	136 734/248
> 170 DDD	1.13 [0.97; 1.33]	125 954/244
NDMA exposure		
Possible (contaminated valsartan batches < 75%)	1.18 [1.01; 1.39]	104 433/232
Probable (contaminated valsartan batches ≥ 75%)	1.15 [1.01; 1.31]	280 734/504
Long-term valsartan use[*2]		
No exposure	1.00 (ref)	61 236/102
Exposure	1.22 [0.80; 1.89]	13 876/28
	Incidence rate per 100 000 person-years[*3]	
No exposure	34.61	
Exposure	39.08	

[*1] Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use

[*2] Long-term valsartan use is defined as valsartan prescription in at least nine quarters within the first 3 years of the study period.

[*3] Standardized to the German population over 40 years in 2011 (e2)

DDD, Defined daily dose; NDMA, N-nitrosodimethylamine; 95% CI, 95% confidence interval

NDMA-contaminated valsartan for more than 3 years.

Biological background

NDMA is classified by the IARC as probably carcinogenic (group 2A). It is carcinogenic in the tissues of experimental animal species with metabolism similar to that of human tissues (9, 15). Ingested NDMA is metabolized by cytochrome P450-dependent mixed-function oxidases to methyldiazonium ions, which alkylate proteins, DNA, and RNA (16–19). In experimental animals oral NDMA exposure increases tumor incidences in various organs, predominantly in the liver (19). Those effects become measurable at doses of about 10 µg/kg/day (19). In our study, exposure to NDMA elevated liver cancer risk independent of dose. This might support the hypothesis of a threshold dose for the development of cancer. NDMA can be found among other N-nitroso compounds in foods, especially those that are smoked or dried at high temperature (20). Epidemiological studies investigating the association between explicit dietary NDMA exposure and cancer yielded inconclusive results (21–23). No inferential statistical analyses were available on the association between human NDMA exposure and liver cancer. Nevertheless, exposure to NDMA-rich food in regions with high liver cancer rates in Thailand could potentially be based on a correlation, although no conclusive studies have been published (24). The observed rates of cancer overall and liver cancer in our study were around 1.5–2 times the national average. This is most likely due to the inclusion of persons aged 40 years and older for analysis, resulting in a study population older than the general population. The effect of NDMA exposure on liver cancer is a statistical result. However, molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans. It may be that NDMA exposure promotes cancer development in already existing, as yet undiagnosed early stages and thus hastens clinical manifestation.

Regulatory and public health implications

Our study provides information for regulatory authorities worldwide to assess the public health impact of NDMA contamination in valsartan drug products. It is an example of how extensive real-world data from statutory health insurance funds can be used to examine urgent drug safety questions with pharmacoepidemiological methods. The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities worldwide was necessary in order to protect public health. The detection of different nitrosamine impurities in drug products since 2018 led to the introduction of a new threshold by the European Medicines Agency (25).

Conclusion

We examined the association of NDMA-contaminated valsartan drug products and cancer risk in a large health insurance data set including more than 780 000 persons. We detected a small, yet statistically significant increase in the risk for liver cancer with the use of NDMA-contaminated valsartan while no association was found for overall cancer risk or other examined single cancer outcomes. However, the present study can only state the existence of a statistical association. Causality cannot be inferred. Long-term effects of regular use of potentially NDMA-contaminated valsartan for more than 3 years could not be evaluated because of the currently still relatively short follow-up time. Therefore, careful monitoring of potential further effects of NDMA-contaminated valsartan after longer periods is advisable.

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Data sharing statement
The data cannot be shared with or transmitted to third parties due to legal restrictions.

Conflict of interest statement
The authors declare that no conflict of interest exists.

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TABLE 3

Risk of individual cancers owing to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

Exposure to NDMA-contaminated valsartan	Hazard ratio [95% CI][*1]	Sample size/ Cancer outcomes
Outcome bladder cancer		
No exposure	1.00 (ref)	355 225/ 1041
Exposure	1.02 [0.95; 1.11]	385 922/ 1491
Outcome breast cancer		
No exposure	1.00 (ref)	208 262/ 1804
Exposure	1.02 [0.96; 1.08]	242 778/ 2736
Outcome colorectal cancer		
No exposure	1.00 (ref)	356 208/ 2024
Exposure	0.99 [0.94; 1.05]	387 297/ 2866
Outcome kidney cancer		
No exposure	1.00 (ref)	354 980/ 796
Exposure	0.96 [0.87; 1.05)	385 522/ 1091
Outcome lung cancer		
No exposure	1.00 (ref)	355 891/ 1707
Exposure	0.97 [0.91; 1.03]	386 710/ 2279
Outcome malignant melanoma		
No exposure	1.00 (ref)	354 934/ 750
Exposure	0.94 [0.85; 1.03]	385 414/ 983
Outcome pancreatic cancer		
No exposure	1.00 (ref)	354 897/ 713
Exposure	0.93 [0.84; 1.02]	385 398/ 967
Outcome prostate cancer		
No exposure	1.00 (ref)	149 514/ 1788
Exposure	1.00 [0.94; 1.06]	146 768/ 2379
Outcome uterine cancer		
No exposure	1.00 (ref)	206 944/ 486
Exposure	1.08 [0.96; 1.21]	240 801/ 759

[*1] Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use

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Corresponding author
Prof. Dr. rer. nat. Britta Haenisch
Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn, Germany
britta.haenisch@bfarm.de

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▶ **Supplementary material**

eReferences, eMethods, eTables, eFigure:
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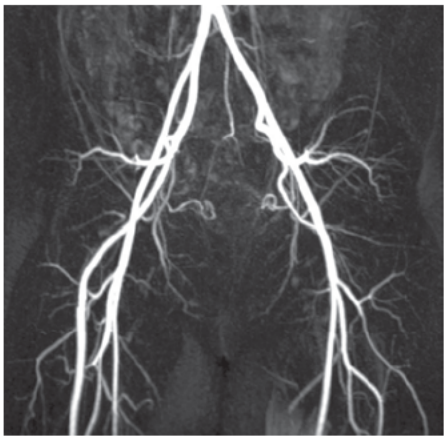
CLINICAL SNAPSHOT

A Rare Cause of Intermittent Claudication: Persistent Sciatic Artery

A 45-year-old female presented with claudication of the right lower extremity. Her ankle-brachial index (ABI) had dropped to 0.6. Angiography revealed an atypical course of the superior femoral artery without transitioning into the popliteal artery. The latter filled with contrast via collaterals in a delayed manner. We suspected a vascular anomaly. After probing the internal iliac artery, it was possible to pass a thrombotically occluded sciatic artery. We initiated local thrombolysis with 1 mg rtPA/h for 20 h. Follow-up angiography showed decreased thrombus burden with underlying stenosis of the vessel. This was treated with a stent. Angiographic magnetic resonance imaging (MR angiography) 6 days following intervention revealed continuity of the schiatic artery *(Figure)*. Follow-up at 12 weeks showed normal ABI without reduced walking distance. Persistent sciatic artery is a rare anatomical variant that arises from the inferior iliac artery and normally regresses in favor of the femoral arteries. Due to poor vessel structure, the vessel is prone to vasculopathy.



MR angiography showing a right persistent sciatic artery.

PD Dr. med. Daniel Kretzschmar, PD Dr. med. Sven Möbius-Winkler, Klinik für Innere Medizin I, Universitätsklinikum Jena, daniel.kretzschmar@med uni-jena.de

PD Dr. med. Rene Aschenbach, Institut für Diagnostische und Interventionelle Radiologie, Universitätsklinikum Jena

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Supplementary material to:

N-Nitrosodimethylamine–Contaminated Valsartan and the Risk of Cancer

A Longitudinal Cohort Study Based on German Health Insurance Data

Willy Gomm, Christoph Röthlein, Katrin Schüssel, Gabriela Brückner, Helmut Schröder, Steffen Heß, Roland Frötschl, Karl Broich, Britta Haenisch

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eReferences

e1. Abdel-Tawab M, Gröner R, Kopp T, Meins J, Wübert J: Valsartan. ZL findet NMDA in Tabletten. Pharm Ztg 2018; 163: 2072–74.

e2. Statistische Ämter des Bundes und der Länder: Zensus 2011. 2014. ergebnisse zensus2011.de/#StaticContent:00,BEV_10_1,m,table (last accessed on 31 July 2020).

eMETHODS

Sample and data source

The data set from the AOK includes information on age, gender, outpatient and inpatient diagnoses (coded using the International Classification of Diseases, 10th revision with German modification, ICD-10-GM) and filled drug prescriptions (categorized according to the Anatomical Therapeutic Chemical classification system ATC code) on a quarterly basis for the years 2009–2017. During the period 2009–2017, on average nearly 25 million persons were insured by the AOK each year.

Selection criteria and diagnoses

Patients were continuously insured by the AOK during the years 2009–2013. Any diagnosis of cancer (ICD C00 to C97, except C44) in the years 2009–2013 led to exclusion from analysis. This ensures that only incident cancer cases occurring in 2014 or later are detected, since the likelihood of recurrence of cancer after 5 years or more without an intervening cancer diagnosis is considered low.

New cancer diagnoses were considered valid if they were main or secondary hospital diagnoses or were documented in the outpatient sector as verified or "status post" diagnoses. For the outpatient diagnoses, at least one confirmatory diagnosis within the following four quarters was required for validation. For the analysis of selected cancer diagnoses (bladder, breast, colorectal, kidney, liver, lung, melanoma, pancreatic, prostate, and uterine cancer) the cancer type had to be the first valid cancer diagnosis. Diagnoses of other cancer types were present only in the index quarter itself or later. The index quarter was defined as the quarter with the first valid cancer diagnosis following the cancer-free period from 2009 to at least the end of 2013. Persons with other cancer diagnoses before the index quarter in which the examined cancer type was diagnosed were not included in the analysis for the specific individual cancer types. The *eFigure* provides an overview of the study cohort for evaluation after application of the selection and quality control criteria.

Exposure

The NDMA content of valsartan tablets seems to correlate with the dose strength of the tablet (e1). Therefore, the valsartan doses of the contaminated drug products can be used to categorize NDMA exposure.

All users had a filled prescription of valsartan within the observation period. The observation period concluded at the end of 2017 at the latest. Prevalent valsartan use was defined as a filled valsartan prescription in the first quarter of 2012. Incident use started at the time of the first filled prescription during the study period. Patients were considered as exposed from the first filled prescription until the end of the observation period.

The marketing authorization holders provided batch-related data on all valsartan drug products for the years 2012–2017. This included detailed information on which batches were manufactured using the active ingredient valsartan supplied by Zhejiang Pharmaceuticals and how many packages of these drug products were sold. Based on this information, we calculated the proportion of all packages of valsartan drug products sold made up by packages manufactured using contaminated ingredients. We calculated this ratio for all pharmaceutical registration numbers (PZN) affected by the recalls of valsartan drug products. We were thus able to divide the PZN into possibly contaminated (< 75% of sold packages with contaminated valsartan) and probably contaminated (≥ 75% of sold packages with contaminated valsartan). It was also possible to calculate the amount of the defined daily dose (DDD) of

contaminated valsartan drug products by multiplying the DDDs from the prescriptions with the previously calculated factors.

Because of the varying length of observation time, the use of cumulative doses may introduce bias. Therefore, we used dose categories and calculated the cumulative maximum of the dose as DDD in a given quarter within the observation time. The dose categories comprise the 33.3% and 66.6% percentiles of all non-zero maximum dose values. Dose categories were determined for the data set with a lag time of 1 year (four quarters) and were also used for sensitivity analyses. We calculated the DDD of contaminated valsartan by quarter and divided the patients into three equal groups with lowest, intermediate, or highest exposure based on the quarter of greatest exposure.

For the evaluation of long-term use of valsartan drug products, we used an exposure period of 3 years as baseline. Long-term use was defined as "patients with filled prescriptions in at least nine of the first twelve quarters (3 years) of the study period." Users of uncontaminated valsartan did not receive any prescriptions of possibly or probably contaminated valsartan in the first 3 years and were right-censored at the first quarter in which they received any contaminated valsartan. Thus, for users of uncontaminated valsartan, only time periods of uncontaminated valsartan use were included in the analysis. Users of possibly or probably contaminated valsartan were defined as having filled prescriptions of contaminated valsartan in at least nine of the twelve quarters. Additional use of uncontaminated valsartan was allowed.

Forty-seven percent of patients receiving potentially contaminated valsartan and 67% of patients receiving uncontaminated valsartan received their second prescription of valsartan with the same contamination status in the following quarter. Sixty-nine percent and 88% of patients, respectively, received a repeat prescription within 1 year after the initial prescription or dropped out of the study. Eighty percent of patients receiving contaminated valsartan and 93% of patients receiving uncontaminated valsartan received a second prescription with the same contamination status within 2 years after the initial dose or dropped out of the study.

Covariates

The following time-dependent covariates were included in the statistical analyses as potential influencing factors: age, gender, polypharmacy (defined as prescription of five or more different drugs), comedications that are known or suspected to affect cancer risk, such as low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy. Furthermore, we included the following comorbidities as additional potential influencing factors: diabetes, chronic obstructive pulmonary disease, congestive heart failure, alcohol-related diseases, the Charlson comorbidity index (score), and presence of prevalent valsartan use at the beginning of the study period. Details of ATC and ICD-10 codes are given in *eTable 3*.

Statistical analyses

We applied Cox regression with time-dependent variables. We selected a lag time of 1 year, since short-term exposure is unlikely to modify the risk of cancer. For sensitivity analysis, we varied the lag time from 6 months to 2 years. In addition, there was a minimal observation time of 1 year before the lag time. For the evaluation of long-term use of valsartan drug products, patients with continuous valsartan prescription for at least 3 years were considered.

All calculations were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and were independently confirmed with R version

3.5.1. Any p-value < 0.05 (two tailed) was considered statistically significant. Hazard ratios (HR) are reported with 95% confidence intervals. Incidence rates were standardized using the 2011 German census for persons aged 40 years and over (e2).

eTABLE 1

Overall cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

	Hazard ratio [95% CI][*1]	Sample size/ cancer cases
Exposure to NDMA-contaminated valsartan		
No exposure	1.00 (ref)	371 688/17 504
Exposure	1.00 [0.98; 1.02]	409 183/24 752
Exposure in dose categories		
0 to ≤ 90 DDDs	1.00 [0.97; 1.03]	130 684/8449
> 90 to ≤ 170 DDDs	1.01 [0.99; 1.04]	144 876/8390
> 170 DDDs	0.98 [0.95; 1.00]	133 623/7913
NDMA exposure		
Possible NDMA exposure (contaminated valsartan batches <75%)	1.00 [0.97; 1.03]	111 962/7761
Probable NDMA exposure (contaminated valsartan batches >=75%)	0.99 [0.97; 1.02]	297 221/16 991
Only prevalent valsartan use[*2]		
No exposure	1.00 (ref)	71 318/5754
Exposure	0.97 [0.94; 1.01]	175 034/12 464
Only incident valsartan use[*2]		
No exposure	1.00 (ref)	300 370/11 750
Exposure	1.01 [0.98; 1.04]	234 149/12 288
Long-term valsartan use[*3]		
No exposure	1.00 (ref)	64 836/3472
Exposure	0.96 [0.89; 1.04]	14 686/817
Exposure in dose categories		
0 to ≤ 90 DDDs	1.00 [0.86; 1.17]	2629/166
> 90 to ≤ 170 DDDs	1.03 [0.89; 1.18]	3777/220
> 170 DDDs	0.91 [0.83; 1.01]	8280/431
	Incidence rate[*4] per 100 000 persons	
No exposure	1254.71	
Exposure	1270.30	

[*1] Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use

[*2] Without covariate "prevalent valsartan use"

[*3] Long-term valsartan use is defined as valsartan prescription in at least nine quarters within the first 3 years of the study period.

[*4] Standardized to the German population over 40 years in 2011 (e2)

DDD, defined daily dose; NDMA, N-nitrosodimethylamine; 95% CI, 95% confidence interval

eTABLE 2

Overall cancer risk and liver cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan, different lag times

	Hazard ratio [95% CI]*	Sample size/ cancer cases
Cancer overall: valsartan prescription		
Lag time 6 months		
No exposure	1.00 (ref)	386 322/19 383
Exposure	1.00 [0.99; 1.02]	443 442/26 375
Lag time 12 months (main analysis)		
No exposure	1.00 (ref)	371 688/17 504
Exposure	1.00 [0.98; 1.02]	409 183/24 752
Lag time 24 months		
No exposure	1.00 (ref)	291 955/11 252
Exposure	0.99 [0.97; 1.01]	371 555/16 966
Liver cancer: valsartan prescription		
Lag time 6 months		
No exposure	1.00 (ref)	367 705/485
Exposure	1.16 [1.04; 1.31]	418 219/774
Lag time 12 months (main analysis)		
No exposure	1.00 (ref)	354 628/444
Exposure	1.16 [1.03; 1.31]	385 167/736
Lag time 24 months		
No exposure	1.00 (ref)	280 990/287
Exposure	1.22 [1.05; 1.41]	355 115/526

* Lag time 1 year, fully adjusted for sex; age; polypharmacy (defined as prescription of five or more different drugs); prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; the comorbidities diabetes, chronic obstructive pulmonary disease, congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (score); and prevalent valsartan use

95% CI, 95% confidence interval

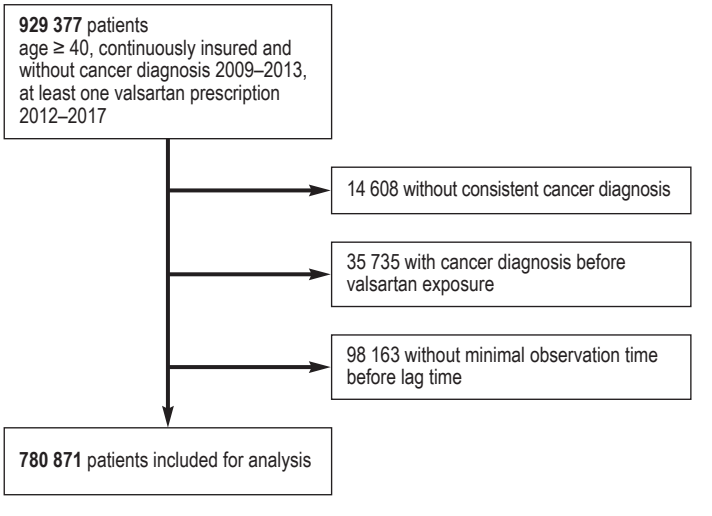
eTABLE 3

ATC codes*[1] and ICD-10 codes*[2]

Substance		
Valsartan	ATC	C09CA03, C09DA03, C09DA23, C09DB01, C09DB08, C09DX01, C09DX02, C09DX04, C09DX05, C09DX10
Acetylsalicylic acid	ATC	B01AC06, B01AC30, B01AC34, B01AC36, B01AC56, B01AC86, C07FX02, C07FX03, C07FX04, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, N02BA01, N02BA51, N02BA71
Non-steroidal anti-inflammatory drugs	ATC	M01A
5α-Reductase inhibitors	ATC	G04CB01, G04CB02, G04CA51, G04CA52
Statins	ATC	C10AA, C10BA, C10BX
Spironolactone	ATC	C03DA01, C03EC01, C03EC21, C03EC41, C03ED01
Glucocorticoids	ATC	H02AB
Hormone replacement therapy	ATC	G03C excl. G03CD, G03DA, G03DB, G03DC, G03EA03, G03F
Selective serotonine reuptake inhibitors	ATC	N06AB, N06CA03
Cancer outcomes		
All cancer	ICD10	C00–C96 excl. C44
Colon cancer	ICD10	C18–C20
Liver cancer	ICD10	C22
Pancreatic cancer	ICD10	C25
Lung cancer	ICD10	C34
Malignant melanoma	ICD10	C43
Breast cancer	ICD10	C50
Uterine cancer	ICD10	C54, C55
Prostate cancer	ICD10	C61
Kidney cancer	ICD10	C64
Bladder cancer	ICD10	C67
Comorbidities		
Diabetes	ICD10	E10–E14
Chronic obstructive pulmonary disease	ICD10	J42–J44
Congestive heart failure	ICD10	I11.0, I13.0, I13.2, I42, I43, I50, I51.7
Alcohol-related disease	ICD10	E244, G31.2, G62.1, G72.1, I42.6, F10.2, K29.2, K70, K86.0, T51.9, Z502, Z72.0

*[1] ATC codes according to the Anatomical Therapeutic Chemical classification system
*[2] ICD-10 codes according to the International Classification of Diseases and Related Health Problems, 10th revision, German modification

eFIGURE



Overview of study cohort after application of the selection and data quality control criteria